

In view of the amendments to the claims, the objections to the claims are overcome. Applicant respectfully requests that the objections to the claims be withdrawn.

Rejection under 35 U.S.C. § 112

In view of the amendment to claim 10, the rejection of claim 14 is overcome. Applicant respectfully requests that the Section 112 rejection of claim 14 be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 2, 5-8 and 10-21 are rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,183,659 to Timoney, et al. ("Timoney I") in view of EP0786515 A1 to Hartford, et al, ("Hartford"), U.S. Patent No. 5,597,807 to Estrada, et al. ("Estrada") and Timoney and Galan, Recent Advances in Streptococci and Streptococcal Diseases, Reedbooks Ltd., 1985: Proceedings of the IXth Lancefield International Symposium on Streptococci and Streptococcal Diseases held in September 1984, pp. 294-5 ("Timoney II"). Applicant respectfully traverses the rejection.

Both Timoney I and II disclose a bacterial vaccine against *Streptococcus equi* (*S. equi*) that stimulated a nasopharyngeal immune response when administered to ponies. The vaccine contained an avirulent strain of *S. equi* (Cornell 709-27) and growth broth (Todd Hewitt broth). Timoney does not disclose the use of saponin or any immunostimulant in the vaccine. Therefore, all that Timoney teaches is that administration of an avirulent strain of *S. equi* induces an immune response.

Timoney is silent as to adjuvants. Certainly, Timoney does not teach or suggest that any adjuvant such as saponin may stimulate mucosal immunity. Consequently, it is not obvious from Timoney to use saponin in combination with *S. equi*. Absent any suggestion that an adjuvant, or saponin in particular, has immunostimulatory properties, and that such adjuvant would provide a protective

immune response to challenge to disease, one of skill in the art would not be motivated to modify Timoney in order to arrive at the claimed invention.

Hartford and Estrada do not remedy the deficiencies in Timoney. Hartford lists saponin as only one among many adjuvants that generally might be included in an *S. equi* vaccine. Hartford does not teach or suggest that any adjuvant stimulates mucosal immunity. Hartford certainly does not teach or suggest to one of skill in the art that saponin is an immunostimulatory adjuvant.

Estrada also fails to provide the required teachings to render the claimed invention obvious. Estrada teaches that saponin surprisingly stimulated an immune response when administered mucosally. However, Estrada does not teach or suggest that saponin provided protection from infection in the face of challenge. Critically, Estrada did not use *S. equi* or any comparable antigen. Thus, Estrada does not teach or suggest that an immune response may be achieved using the combination of saponin and *S. equi* or a comparable bacterial or disease causing antigen.

Clearly, the combination of references does not render the claimed combination of *S. equi* and saponin obvious. It appears that the Examiner has improperly applied hindsight reasoning to the cited combination of references in order to support the obviousness rejection. *Grain Processing Corp. v. American Maize-Products Corp.*, 840F2d 902, 907; 5 USPQ2d 1788,1792 (Fed. Cir. 1988). The Court in *Grain Processing* held that:

Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of the prior art references, combining the right references in the right way so as to achieve the results of the claims in suit.

840 F2d. at 902.

One of skill in the art would, at best, only be motivated to combine Hartford and Estrada with Timoney based on the present invention because Timoney is silent as to the use of any adjuvants. Applicant submits that it would not have been

obvious that any adjuvant would provide the enhanced protective immunological effect demonstrated by the claimed saponin/attenuated *S. equi* vaccine.

Nevertheless, applicant has provided herewith the Declaration of Wumin Li, Ph.D. which provides evidence that it would not be obvious to combine an avirulent strain of S. equi with saponin to obtain an S. equi vaccine which induces an immune response.

The Declaration of Dr. Li also provides evidence that it would not have been obvious that an S. equi vaccine would have induced protective immunity in horses based on the results in a mouse model that showed that an S. equi vaccine stimulated an immunological response in mice.

In addition, the Declaration of Dr. Li provides evidence that it would not have been obvious that a protective immune response would be obtained upon administration of an S. equi vaccine if antibodies are produced in response to administration of the S. equi vaccine.

In Dr. Li's opinion, it would not have been obvious to combine an avirulent strain of S. equi with saponin to obtain an S. equi vaccine which induces a protective immune response because at the time of the invention, the efficacy of saponin as an adjuvant was not predictable. Based on knowledge at the time of the invention, one of skill in the art could not predict that saponin would be consistently potent. At the time of the invention, one of skill in the art would not be able to predict that saponin would be equally effective as an adjuvant across species. Thus, it would not have been predictable that saponin would enhance the immunogenicity of a vaccine in all species if it was shown to do so in one species.

Dr. Li states that one of skill would not have selected saponin over other adjuvants, such as those disclosed by Hartford because saponin was known to have adverse side effects, such as adverse biological effects, e.g., severe tissue injury or inflammation. Therefore, one of skill would not have predicted that saponin would not have biological side effects (toxicity) to the vaccinated subject. One of skill also would

not have been able to predict that saponin would not have an adverse effect on the infectivity and immunogenicity of antigens.

In Dr. Li's opinion, at the time of the invention, one of skill in the art would not have been able to predict that saponin would be effective as an adjuvant with any antigen. The adjuvant activity of saponin is dependent upon the particular antigen used and the immunogenicity of the antigen. One of skill in the art would know that not all adjuvants have the same efficacy. One of skill in the art at the time of the invention would not have been able to predict that saponin would induce an immune response or enhance the immunogenicity of an antigen. Thus, without testing the particular combination of a target antigen and saponin, one would not be able to predict that saponin would be an effective adjuvant or that it would not have a detrimental effect on the immunogenicity of the antigen. However, that it might have been "obvious to try" saponin and *S. equi* in a vaccine is not a legitimate basis for an obviousness rejection. *In re Fine*, 5 USPQ2d 1596,1599 (Fed. Cir. 1988).

Based on the foregoing, it would not have been obvious to combine an avirulent strain of *S. equi* with saponin to obtain an *S. equi* vaccine which induces an immune response.

In Dr. Li's opinion, it also would not have been obvious that an *S. equi* vaccine would have induced protective immunity in horses based on the results in a mouse model that showed that an *S. equi* vaccine stimulated an immunological response in mice.

The Examiner asserts that Timoney and Hartford teach that the mouse model is routinely used to establish the protective effect of vaccines in horses. However, one of skill in the art would interpret the results of studies in mice reported by Timoney and Hartford as only teaching that there was an immunological response in the mice to the *S. equi*. One of skill would not have extrapolated the data in mice to conclude or suggest that there would be a similar effect in horses.

In Dr. Li's opinion, based on the state of the art at the time of the invention, as evidenced by the state of the art even as of 1999, immunological parameters could not have been extrapolated to the horse from the effects of the vaccine observed in the mouse model.

Thus, the Examiner's assertion that the claimed vaccine would intrinsically provide protective immunity in horses is not supported by the teachings of the references nor the state of the art at the time of the invention.

In addition, in Dr. Li's opinion, it would not have been obvious that a protective immune response would be obtained upon administration of an S. equi vaccine if antibodies are produced in response to administration of the S. equi vaccine.

The Examiner asserts that, in view of Estrada, it would have been obvious that the combination of saponin and *S. equi* would elicit a protective immune response because Estrada teaches that administration of saponin increased IgG and IgA levels.

However, in Dr. Li's opinion, an immunological response is not predictive of protective immunity in the face of challenge. Based on the state of the art at the time of the invention, and even as of 1998, one of skill in the art would not have been able to predict from the level of antibody detected in an animal's serum after vaccination whether the vaccine provided a protective immune response.

If the levels of antibodies are not predictive of protective immunity, then one of ordinary skill in the art would not expect to enhance the protective effect of a vaccine with an adjuvant that had not been shown to be protective, and certainly would have no reasonable expectation that this could be achieved. Thus, the teaching of Estrada that the saponin causes increased absorption through mucosal membranes does not teach or suggest that saponin stimulates protective mucosal immunity when the animal is challenged with an infective organism.

Based on the knowledge that an immune response is not predictive of a protective response, and in view of the limited teachings of the cited references, discussed above, one of skill certainly could not predict that the use of saponins in a vaccine with attenuated *S. equi* would enhance a specific immunostimulatory protective response to challenge with disease, such as challenge by wild type *S. equi*. The combination of references does not suggest or motivate one of skill to use saponin in an *S. equi* vaccine as an immunostimulant. Therefore, the combination of cited references does not render the claimed invention obvious.

In view of the foregoing, applicant respectfully submits that the rejection of the claims under Section 103 cannot stand and respectfully requests that the rejection be withdrawn.

CONCLUSION

In view of the foregoing amendment and comments, applicant submits that the claims are in form for allowance. A notice to that effect is hereby solicited.

Respectfully submitted,



Raina Semionow
Reg. No. 39,022
Attorney for Applicant

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

::ODMA\WORLD\OX\M:\0632\0D916\RXS1137.WPD